

Occupational asthma caused by natural rubber latex: Outcome according to cessation or reduction of exposure

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Background: The long-term effects of reducing exposure to latex in subjects with latex-induced asthma remain unknown. **Objective:** The purpose of this study was to compare the health and socioeconomic outcomes of subjects with latex-induced asthma before and after reduction or cessation of exposure to latex.

Methods: Thirty-six subjects with latex-induced asthma as ascertained by specific inhalation challenges were investigated after a median follow-up of 56 months (range, 12 to 92 months). Initial and follow-up visits included use of a detailed questionnaire and measurement of the concentration of histamine causing a 20% fall in FEV₁ (PC₂₀). At follow-up, information on employment, financial status, and quality of life was collected.

Results: At follow-up, 16 subjects were no longer exposed to latex, whereas 20 subjects had reduced exposure. In the subjects who avoided exposure, asthma severity decreased from a median score of 8.5 to 3.5 ($P = .001$) and the median histamine PC₂₀ value increased from 0.4 mg/mL to 2.3 mg/mL ($P = .002$). In the subjects who reduced their exposure, asthma-severity score improved from 6.5 to 2.5 ($P < .001$) and PC₂₀ values rose from 0.5 mg/mL to 2.4 mg/mL ($P < .001$). Cessation of exposure to latex was associated with asthma-related work disability (69%) and loss of income (62%) more frequently than was reduction of exposure (35% and 30%, respectively).

Conclusion: Reduction of exposure to latex should be considered a reasonably safe alternative that is associated with fewer socioeconomic consequences than removal from exposure. (*J Allergy Clin Immunol* 2002;109:125-30.)

Key words: Asthma, disability, latex, occupational lung disease

Over the last decade, exposure to airborne natural rubber latex has emerged as a major cause of respiratory allergy among exposed workers,¹ and it is now the fourth-most-common cause of occupational asthma reported to the Surveillance of Work-related Occupation-

Abbreviations used

LOA: Latex-induced occupational asthma

NSBH: Nonspecific bronchial hyperresponsiveness

al Respiratory Disease surveillance program.² Complete avoidance of exposure to airborne latex is extremely difficult to implement, inasmuch as latex allergens are readily disseminated through their binding onto cornstarch glove powder. Widespread substitution of synthetic gloves for latex gloves has raised concerns about the cost of nonlatex gloves, their protective properties, and their tactile quality.³ Personal use of latex-free gloves by latex-allergic subjects has been associated with decreases in allergic symptoms and serum latex-specific IgE levels,⁴ though this is not likely sufficient to prevent inhalation of latex allergens and the development of asthmatic reactions if coworkers continue to wear powdered latex gloves. Low-allergen and/or powder-free latex gloves are effective in lowering the release of airborne allergens⁵⁻⁹ and the risk of developing asthmatic reactions in subjects with latex-induced occupational asthma (LOA).^{5,8-10}

The objective of this study was to explore the long-term health and socioeconomic consequences of LOA as impacted by reduction in or total avoidance of exposure to latex allergens.

METHODS

Subjects

The study included 36 subjects who met the following criteria: (1) a diagnosis of LOA had been confirmed by specific inhalation challenge with latex gloves; (2) an initial assessment of lung function tests within 48 hours of exposure to the causative workplace was available; (3) the subject had either completely avoided or markedly reduced exposure to airborne latex at follow-up; and (4) the duration of follow-up since the initial examination was at least 12 months. The subjects were initially referred to our center either by the Workers' Compensation Board (Fonds des Maladies Professionnelles) or by their attending physicians. Five subjects had been identified through a prevalence survey of LOA in a primary-care hospital.¹¹ A total of 44 patients had been diagnosed as having LOA between March 1993 and May 2000. Eight subjects were not enrolled in this follow-up study, the reasons being as follows: (1) 2 subjects declined to participate in the study; (2) 3 subjects could not be initially assessed within 48 hours of workplace exposure because they had already left their jobs; (3) 1 subject died from a nonrespiratory disease; (4) 1 subject was pregnant at the time of the follow-up study; and (5) 1 subject remained permanently exposed to large numbers of powdered latex gloves at the follow-up visit.

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Supported by the Services Fédéraux des Affaires Scientifiques, Techniques et Culturelles, Programme d'appui scientifique à la protection des travailleurs (grant SSTC PS/10/44).

Received for publication August 10, 2001; revised October 1, 2001; accepted for publication October 1, 2001.

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0091-6749/2002 \$35.00 + 0 1/86/120760

doi:10.1067/mai.2002.120760

Study protocol

The initial and follow-up assessments were performed at a median interval of 56 months (25th-75th percentiles, 32-82 months). Each visit included the completion of a detailed medical and occupational questionnaire as well as spirometry and measurement of nonspecific bronchial hyperresponsiveness (NSBH). The initial assessment also included skin prick testing with a commercial latex extract and 21 common inhalant allergens (Stallergènes, Waterloo, Belgium) and specific inhalation challenges with latex gloves.¹² The protocol and procedures of the study were approved by the Ethics Committee of Mont-Godinne Hospital. Each participant was informed of the purposes and procedures of the follow-up study and signed a statement of informed consent.

Questionnaire

The questionnaire administered at the initial and follow-up visits was designed to collect information on the following items: (1) occupational history; (2) smoking habits and history of atopic disease; (3) severity of asthma, as assessed by the frequency of symptoms, use of anti-asthma treatment, and hospital or emergency department admissions; (4) severity of rhinitis, as reflected by the frequency of symptoms and need for medication; and (5) history of allergic reactions to foods and anaphylactic reactions.

Exposure to airborne latex was assessed qualitatively through use of job descriptions (ie, type and number of gloves used by the subjects and their coworkers) and available information on airborne latex allergen measurements.⁶ At the time of the initial evaluation, either the subjects had not worn latex gloves for months or years or they had worn them only occasionally (to prevent contact urticaria); however, they remained exposed to airborne latex generated by their coworkers and continued to be symptomatic at work. After the diagnosis of LOA was established, the subjects were advised to strictly avoid exposure to latex, whether direct or indirect. When complete avoidance was not feasible, strategies aimed at reducing exposure to airborne latex were explained to the subjects and, when necessary, to their occupational health physicians or workplace executives. A subject was included in the "cessation of exposure" group when latex gloves were never used in his or her working environment; a subject was included in the "reduction of exposure" group when (1) less than 20 pairs of latex gloves were used per week in the room or department where he or she worked or (2) only low-allergen sterile gloves were used, together with latex-free examination gloves.

The severity of asthma at the initial and follow-up assessments was graded through use of a score proposed by Blanc et al¹³ for assessing work disability among adults with asthma; this score (ranging from 0 to 28) is based on hospital admissions, frequency of asthma symptoms, and use of asthma medications. At the follow-up visit, we also collected information on the number of medical visits due to asthma over the last 12 months. We assessed the severity of rhinitis by constructing a 12-point score derived from the addition of the following items: (1) frequency of rhinitis symptoms (0 = never, 1 = less than once a week, 3 = more than once a week but less than once a day, and 4 = everyday); (2) administration of a nasal spray (decongestants, antihistamines, or topical steroids) (same gradation); and (3) use of oral antihistamines (same gradation).

At the follow-up visit, the questionnaire inquired into the socioeconomic consequences of LOA, including the following: (1) current working status, job changes, and periods of unemployment due to asthma since the initial visit; (2) perceived income changes (unchanged, slightly decreased, markedly decreased); (3) actual magnitude of earning loss; and (4) compensation status. Asthma-related work disability was defined as having changed jobs or ceased to work because of asthma.¹⁴ The impact of asthma on quality of life was investigated through use of the French version of the standardized self-

administered questionnaire (AQLQ) developed by Juniper et al.¹⁵ In addition, each subject was asked to provide a global assessment of the impact of LOA and latex allergy on his or her professional activities, social intercourse, and family life. This impact was graded through use of a scale from 0 (no impairment) to 7 (marked impairment).

Lung function assessment

At both visits, spirometry was performed and NSBH was measured within 48 hours of exposure to the workplace. Both assessments were performed at the same time of the year (± 1 month) to minimize the influence of exposure to common aeroallergens. Lung function tests were carried out after appropriate withdrawal of medications. The patients had to be free of acute respiratory infection for at least 4 weeks before examination. FEV₁ and forced vital capacity were measured according to the recommendations of the American Thoracic Society¹⁶ through use of a pneumotachograph instrument (Medisoft, Dinant, Belgium). Predicted values were those of the European Community for Coal and Steel.¹⁷

NSBH was assessed by having the subject inhale doubling concentrations of histamine (0.0125 to 32 mg/mL) at tidal breathing, according to the method described by Cockcroft et al.¹⁸ The level of NSBH was expressed as the concentration of histamine causing a 20% fall in FEV₁ (PC₂₀). PC₂₀ values less than 16 mg/mL were considered to reflect significant bronchial hyperresponsiveness. Changes in PC₂₀ greater than 3-fold from the initial to the follow-up visits were considered significant, inasmuch as this corresponds to the 95% CI for the between-day, within-subject reproducibility of the test in our laboratory.¹⁹

Specific inhalation challenges

Specific inhalation challenges with latex gloves were carried out according to a previously described protocol.^{11,12} Briefly, after a control challenge with vinyl gloves, the subjects were asked to handle powdered latex gloves for gradually increasing periods of time until FEV₁ fell by more than 20% or until a cumulative exposure of 4 hours was completed on 2 consecutive days.

Analysis of results

Data are presented as medians with 25th and 75th percentiles. Changes in clinical and functional features between initial and follow-up assessments were evaluated by means of McNemar or binomial tests for categorical variables and by means of Wilcoxon signed-rank test for numeric and ordinal variables. Subjects who were no longer exposed to latex were compared with those who had reduced exposure through use of χ^2 tests, Fisher exact tests, or Wilcoxon rank sum tests, as appropriate. Multivariate logistic regression analysis with backward selection of variables by Wald testing was carried out to explore the determinants of a significant improvement (>3 -fold increase) in the histamine PC₂₀ value at follow-up. This analysis included the following independent variables: duration of asthma symptoms at work; duration of exposure to latex gloves; duration of follow-up; atopy; asthma before employment; asthma-severity score; treatment with inhaled steroids. Analysis was performed through use of SPSS 10.0 statistical software (SPSS Inc, Chicago, Ill). All tests were 2-tailed. The level of statistical significance was set at a *P* value of less than .05.

RESULTS

Baseline characteristics

The subjects who ceased exposure to latex did not differ from those with reduced exposure for most demographic features (Table I). There were no differences between cessation and reduction of latex exposure with regard to clinical and functional characteristics at the ini-

TABLE I. Baseline demographic and clinical characteristics of the subjects

	Cessation of latex exposure (n = 16)	Reduction of latex exposure (n = 20)
Female sex: n (%)	15 (94)	17 (85)
Age* (y)	32 (29-36)	32 (30-35)
Occupation: n (%)		
Health care workers	11 (69)	19 (95)
Non-health care workers	5 (31)	1 (5)
Smokers and exsmokers: n (%)	2 (12)	2 (10)
Positive skin test results to aeroallergens: n (%)		
House dust mites	5 (31)	7 (35)
Pets	5 (31)	8 (40)
Tree pollens	3 (19)	2 (10)
Grass pollens	5 (31)	6 (30)
Weed pollens	1 (6)	3 (15)
Molds	2 (12)	2 (10)
At least 1 allergen (atopy)	9 (56)	14 (70)
Asthma before employment: n (%)	3 (19)	8 (40)
Referral by WCB: n (%)	6 (38)	6 (30)
Duration of exposure before onset of LOA* (mo)	68 (12-112)	73 (42-102)
Duration of asthma before diagnosis* (mo)	78 (42-120)	94 (49-125)
Time lapse from first symptom of latex allergy to onset of LOA* (mo)	8 (4-14)	6 (2-36)
Duration of follow-up* (mo)	50 (26-82)	60 (32-83)
Type of asthmatic reaction elicited by SIC: n (%)		
Immediate	7 (44)	14 (70)
Dual	7 (44)	5 (25)
Isolated late	2 (12)	1 (5)
Duration of exposure causing an asthmatic reaction during SIC* (min)	60 (25-101)	112 (22-180)

WCB, Workers' Compensation Board; SIC, specific inhalation challenge with latex gloves.

*Median with 25th-75th percentiles in parentheses.

tial visit (Tables II and III). At the initial assessment, however, continuous treatment with inhaled steroids was more frequent among subjects who subsequently avoided exposure to latex (11/16) than among those who reduced their exposure (4/20; $P = .003$).

Health outcomes

At the follow-up visit, asthma severity scores improved significantly and similarly in both groups, though the proportion of subjects still requiring inhaled steroids on a regular basis was higher among those who had ceased exposure to latex (8/16) than among those who had reduced exposure (3/20; $P = .023$; Table II). FEV₁ improved significantly only in subjects who reduced exposure to latex, from 93% (range, 91% to 96%) to 100% (range, 92% to 108%) of predicted ($P = .009$; Table III). The level of NSBH improved significantly from the initial assessment to the follow-up assessment in both groups (Table III). The median PC₂₀ value increased from 0.4 to 2.3 mg/mL ($P = .002$) in subjects who were no longer exposed to latex and from 0.5 to 2.4 mg/mL ($P = .001$) in those with reduced exposure. The mean of differences in PC₂₀ values between the initial and follow-up visits was similar in the 2 groups. A significant (>3-fold) increase in histamine PC₂₀ value was observed in 8 (50%) of the subjects without exposure to latex and in 15 (75%) of those with reduced exposure. Only 1 subject (with reduced exposure) showed a normal level of PC₂₀ at the follow-up examination.

Logistic regression analysis showed that a low asthma severity score at the initial assessment was the only significant ($P = .009$) predictor for a 3-fold increase in histamine PC₂₀ value at the follow-up visit.

The rhinitis-severity score decreased markedly in subjects who avoided exposure as well as in those who reduced exposure (Table II). Allergy to fruits known to cross-react with latex allergens was a common occurrence among our subjects, regardless of whether they remained exposed to latex at work. At the initial visit, 14 subjects (39%) reported allergic symptoms after ingestion of fruits, including 5 subjects with cessation of exposure and 9 subjects with reduced exposure. During the follow-up period, an additional 11 subjects reported the onset of fruit allergy while they avoided ($n = 6$) or reduced ($n = 5$) workplace exposure to latex. These new-onset allergic manifestations occurred 2 to 74 months after the initial visit (median interval, 19 months; 25th-75th percentiles, 10-34 months). Seven of the 14 initially allergic subjects developed allergy to other fruits during the follow-up period (3 subjects with cessation of exposure and 4 with reduced exposure). At follow-up, 25 (69%) of our subjects reported having experienced 43 episodes of fruit allergy, including isolated oral syndrome ($n = 26$), urticaria with mild respiratory symptoms ($n = 10$), and urticaria or angioedema associated with severe upper or lower respiratory symptoms ($n = 7$). None of the subjects reported a progression from mild to severe reactions, probably because they were instructed

TABLE II. Symptoms and treatment at initial and follow-up visits

	Cessation of latex exposure (n = 16)	Reduction of latex exposure (n = 20)	P value*
Asthma severity score†			
Initial visit	8.5 (7.0-9.8)	6.5 (5.0-9.5)	
Follow-up visit	3.5 (1.2-6.8)‡	2.5 (1.0-5.0)‡	
Inhaled steroids at initial visit: n (%)			
None or intermittent	5 (31)	16 (80)	
Continuous	11 (69)	4 (20)	.003
Inhaled steroids at follow-up visit: n (%)			
None or intermittent	8 (50)	17 (85)§	
Continuous	8 (50)	3 (15)§	.023
No. of asthma-related medical visits‡	2 (0-9)	0 (0-2)	.031
No. of asymptomatic subjects without treatment at follow-up: n (%)	3 (56)	4 (20)	
Rhinitis severity score†			
Initial visit	8.0 (7.0-9.0)	6.5 (5.2-9.0)	
Follow-up visit	2.0 (1.0-6.2)‡	2.5 (2.0-4.0)‡	

*When reduction and cessation of exposure to latex were compared.

†Median with 25th-75th percentiles in parentheses.

‡ $P \leq .001$ when initial and follow-up assessments were compared.§ $P = .032$ when inhaled steroid treatment at initial and follow-up visits were compared.

||During the last 12 months before follow-up assessment.

TABLE III. Lung function tests at initial and follow-up visits

	Cessation of latex exposure (n = 16)	Reduction of latex exposure (n = 20)	P value*
FEV ₁ : percent predicted†			
Initial visit	96 (91-106)	93 (91-96)	
Follow-up visit	99 (91-110)	100 (92-108)§	
Histamine PC ₂₀ † (mg/mL)			
Initial visit	0.4 (0.1-1.0)	0.5 (0.1-1.0)	
Follow-up visit	2.3 (0.5-5.8)‡	2.4 (1.0-6.6)‡	
Level of NSBH at initial visit: n (%)			
PC ₂₀ = 2 to 16 mg/mL	2 (12)	1 (5)	
PC ₂₀ = 0.25 to 2 mg/mL	9 (56)	13 (65)	
PC ₂₀ < 0.25 mg/mL	5 (31)	6 (30)	
Level of NSBH at follow-up visit: n (%)			
PC ₂₀ > 16 mg/mL	0	1 (5)	
PC ₂₀ = 2-16 mg/mL	9 (56)	11 (55)	
PC ₂₀ = 0.25-2 mg/mL	5 (31)	7 (35)	
PC ₂₀ < 0.25 mg/mL	2 (12)	1 (5)	
Changes in PC ₂₀ at follow-up: n (%)			
>2-fold increase	11 (69)	17 (85)	
>3-fold increase	8 (50)	15 (75)	

*When reduction and cessation of exposure to latex were compared.

†Median with 25th-75th percentiles in parentheses.

‡ $P \leq .002$ when initial and follow-up assessments were compared.§ $P = .009$ when initial and follow-up assessments were compared.

to refrain from eating fruits causing oral itching. However, in the same subject, the severity of allergic reactions varied greatly from one fruit to another. At follow-up, 11 subjects had experienced 13 severe anaphylactic reactions requiring emergency treatment, of which 7 resulted from fruit ingestion, 7 resulted from surgical or medical procedures, and 1 resulted from natural delivery.

Socioeconomic outcomes

Complete avoidance of exposure to latex was associated with a substantial impact on working status (Table IV).

At the follow-up visit, 5 (31%) of 16 subjects were currently not working because of LOA. Asthma-related disability, defined as ever having changed jobs or left work because of asthma symptoms, was more frequent in subjects who ceased exposure (11/16 [69%]) than in subjects who remained exposed to reduced levels of latex (7/20 [35%]; $P = .044$). Sixty-two percent of subjects without exposure to latex reported that they had experienced a reduction in income; this compared with 30% ($P = .042$) of those who had reduced their exposure. The median actual reduction in earnings was 20% (25th-75th per-

TABLE IV. Impact of latex-induced asthma on socioeconomic status and quality of life

	Cessation of latex exposure (n = 16)	Reduction of latex exposure (n = 20)	P value*
Currently working: n (%)	9 (56)	20 (100)	.003
Same job, same employer	3	11	
Same job, different employer	2	3	
Different job, same employer	2	6	
Different job, different employer	2	0	
Not working: n (%)	7 (44)	0	
Unemployed	4	0	
Chronic sick leave	3	0	
Work disruption due to LOA	5 (31)	0	.023
Asthma-related work disability‡	11 (69)	7 (35)	.044
Perceived change in income: n (%)			
Slight reduction	1 (6)	3 (15)	
Major reduction	9 (56)	3 (15)	.042
Actual reduction in income (% from initial value)†	20 (0-51)	0 (0-16)	.038
Quality of life questionnaire			
Symptoms†	4.6 (3.8-5.6)	5.2 (4.3-6.2)	
Activities†	4.5 (3.0-6.0)	5.1 (4.2-5.8)	
Emotions†	5.2 (4.2-6.2)	5.3 (4.6-7.0)	
Environment†	4.7 (3.0-6.2)	5.2 (4.5-6.2)	
Global score†	4.6 (3.6-5.7)	5.2 (4.7-6.0)	
Perceived impact of latex-induced asthma			
Professional activities†	5.0 (3.0-6.0)	3.0 (2.0-4.0)	.033
Social intercourse†	3.0 (2.2-4.0)	2.0 (1.0-3.0)	.013
Family life†	1.5 (1.0-3.0)	1.0 (0.2-2.0)	

*When reduction and cessation of exposure to latex were compared.

†Median with 25th-75th percentiles in parentheses.

‡Defined by changing job or leaving work because of LOA.

centiles, 0% to 51%) in the group without exposure and 0% (25th-75th percentiles, 0% to 16%) in the group with reduced exposure. Among those who reported a reduction in income and who answered the question about compensation benefits, income loss was offset by the Workers' Compensation Board's indemnity in 3 of 7 subjects with cessation of exposure to latex and in 1 of 5 subjects with reduction of exposure. The quality of life did not differ between the 2 groups. However, the perceived impact of LOA on professional activities and social intercourse was more pronounced in subjects who avoided exposure to latex than in those who reduced exposure (Table IV).

DISCUSSION

We found that in the subjects who reduced their exposure to latex, the improvement in asthma and rhinitis symptoms, as well as in the level of nonspecific bronchial hyperresponsiveness, was similar to what was observed in the subjects who avoided exposure to latex. However, removal from exposure was associated with more pronounced work disability, income loss, and perceived impairment of professional and social activities. When compensation benefits were taken into account, the final income loss did not differ between those who avoided exposure and those who reduced exposure. However, compensation data derived from our study cannot be extrapolated to other countries, because compensation varies widely from one country to another.

Several potential limitations of this study should be addressed. A major (though unavoidable) flaw is that subjects were not randomly assigned to "reduction" or "cessation" of exposure. Exposure status resulted from a number of uncontrolled individual and work-related factors, including financial implications of latex-glove substitution and possibilities for relocation to less exposed jobs. Among individual factors, the subject's decision to avoid or reduce exposure to latex might have been affected by the severity of the disease at the time of diagnosis. This assumption is supported by the finding that subjects who ceased exposure showed some features suggesting more severe asthma at initial assessment. They were more often treated with inhaled steroids on a regular basis, though the 2 groups of subjects did not differ with respect to global asthma-severity score, baseline FEV₁, or level of NSBH. This possibility probably also accounts for the finding that those subjects who avoided exposure showed less improvement at follow-up. An increase in FEV₁ at the follow-up visit was documented only in subjects with reduced exposure, though fewer of them had undergone continuous treatment with inhaled steroids. The number of subjects included in this study was not large enough to exclude differences in respiratory outcome with a high level of confidence. Definitive conclusions would require investigation of larger cohorts of subjects with LOA. Finally, we used a qualitative assessment of latex exposure, which focused on indirect exposure to airborne allergens generated by coworkers.

Accordingly, this study does not allow for determining a safe threshold level of exposure to airborne latex allergens for subjects with LOA. It is unlikely, however, that the lack of quantitative environmental assessment would have resulted in misclassification of subjects between reduction and cessation of exposure.

Longitudinal studies of workers with occupational asthma caused by various agents have shown that avoidance of exposure to the causal agent results in improvement in asthma symptoms and functional parameters, though symptoms and NSBH persist in approximately 70% of affected workers.²⁰ These studies have consistently found that persistence of asthma was associated with a longer duration of asthma before removal and with more severe asthma at the time of diagnosis. Therefore, there is general agreement that complete and definitive removal from exposure is the key treatment for occupational asthma.²⁰ However, complete removal from exposure has considerable professional and financial consequences; it is associated with persistent work disruption in 25% to 35% of the subjects as well as with a substantial loss of income.²⁰ Although subjects with occupational asthma removed from exposure have been extensively investigated, only a few studies have explored the long-term effects of reducing exposure to the causal agent.²¹⁻²⁶ These studies are often difficult to interpret, because outcome variables were assessed in different ways—subjects with reduced exposure were not always compared with those who were removed,^{21,24} small numbers of subjects were assessed,²³ or the study design was retrospective.²⁶ Some of these studies indicate that persistence of exposure to low levels of red cedar dust and isocyanates resulted in worsening of asthma symptoms and lung function.^{21,22,25} However, other studies have failed to find a significant difference in the severity of asthma between subjects who had been completely removed and those who had been transferred to lower exposure.^{23,24,26}

Despite its inherent limitations, this study suggests that reduction of exposure to latex represents a reasonably safe alternative that should be considered in workers with LOA when suppression of exposure is not feasible or when the possibilities for nonexposed jobs are limited. Compared with complete removal, reduction of exposure is associated with a substantially lower socioeconomic impact. Cost-benefit analyses comparing these 2 treatment options are required to improve the medical and professional management of occupational asthma.

We thank Lori Schubert for reviewing the manuscript.

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